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Draft – Not for Implementation

Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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Preface

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Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

This guidance, when finalized, is intended to assist drug sponsors and device manufacturers who are planning to develop new antimicrobial drugs and antimicrobial susceptibility test (AST) devices and who seek to coordinate development of these products such that the AST device could be cleared either at the time of new drug approval or shortly thereafter.

Specifically, the guidance intends to accomplish the following:

- Describe interactions between drug sponsors and device manufacturers for coordinated development of a new antimicrobial drug and an AST device;
- Explain the considerations for submitting separate applications to CDER and CDRH when seeking clearance of an AST device coincident with, or soon following, antimicrobial drug approval; and
- Clarify that the review of the new antimicrobial drug product and AST device(s) will remain independent, and that coordinated development does not influence the MDUFA and PDUFA review timelines for either product.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should

be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Antimicrobial susceptibility testing is an important component in supporting the development of new antimicrobial drugs and the subsequent clinical use of these agents. In addition to informing the appropriate clinical use of antimicrobial drugs, antimicrobial susceptibility testing used in epidemiological studies can identify the emergence of drug resistance and monitor overall population changes in antimicrobial susceptibility.

The development of antimicrobial drugs and AST devices that test for in vitro susceptibility of bacterial pathogens isolated from clinical specimens to antimicrobials has traditionally occurred independently, with AST device development often initiated following drug approval. Coordinated development of new antimicrobial drugs with AST devices can potentially minimize the time between the approval of a new antimicrobial drug and clearance of an AST device that tests for in vitro susceptibility of pathogens to that drug product. Coordinated development also offers possible benefits to both the drug sponsor and device manufacturer during the antimicrobial drug and AST device development processes. Drug sponsors may benefit by having access to AST device technology that may be valuable during clinical studies. AST device manufacturers may similarly benefit by having access to clinical samples and isolates obtained during the drug development that may aid in validation of the device. These benefits may be particularly applicable to molecular-based and other devices that infer antimicrobial resistance through the detection of microbial resistance markers.

AST devices are regulated by CDRH. These devices include AST discs,[1] automated AST systems,[2] and other devices used for the testing of in vitro susceptibility of bacterial pathogens to antimicrobial drugs. In general, a premarket notification (510(k)) submission is required for an AST device being introduced into commercial distribution for the first time, or for changes or modifications to a cleared AST device, where the modifications could significantly affect the safety or effectiveness of the device. See sections 510(k), 513(f), and 513(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 CFR 807.81. For example, when seeking to add a new, approved antimicrobial drug to an existing AST panel used with an automated AST system, a 510(k) submission is generally required because this could significantly affect the safety or effectiveness of the device and is a major change or modification to the intended use of the device. 510(k) submissions are typically provided to FDA for such AST devices subsequent to the approval of an NDA for a new antimicrobial drug. The time between NDA approval and submission of a 510(k) for an AST device that incorporates the new antimicrobial drug is primarily due to the time it takes manufacturers to develop and test AST devices with the new antimicrobial drug and time to prepare the necessary regulatory submission. Minimizing the time

[1] 21 CFR 866.1620.
[2] 21 CFR 866.1645.

between approval of new NDAs and clearance of related AST devices would more quickly enable these AST devices to be accessible for clinical use in assessing in vitro pathogen susceptibility. This would also be true for molecular-based or other assays that identify genetic markers or mutations associated with phenotypic resistance as determined by traditional AST device methods.

There are several other FDA guidances that may be of interest to developers of new antimicrobial drug products or AST devices. The guidance "Microbiological Data for Systemic Antimicrobial Drug Products — Development, Analysis, and Presentation," available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM182288.pdf, addresses the microbiological data that FDA recommends be submitted for new antimicrobial drug product development. The guidance "Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems," available at: http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080564.htm, identifies specific risks associated with automated short-term incubation cycle AST systems and describes measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these AST devices prior to marketing such a device. There are also FDA guidances that address related issues, e.g., the development of molecular multiplex assays that may include the detection of resistance markers.

Coordinated development of an antimicrobial drug and an AST device as discussed in this guidance is distinct from the discussion of in vitro companion diagnostic devices in the FDA guidance entitled "In Vitro Companion Diagnostic Devices; Guidance for Industry and Food and Drug Administration Staff," available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf. As described in this guidance, FDA has traditionally not considered microbiology diagnostics to be companion diagnostic devices, i.e., "as an in vitro diagnostic device that provides information that is *essential* for the safe and effective use of a corresponding therapeutic product" (emphasis added).

III. Interactions between Antimicrobial Drug Sponsors and AST Device Manufacturers

FDA encourages antimicrobial drug sponsors and AST device manufacturers to discuss coordinated development opportunities during antimicrobial drug development with each other. These discussions should take place early during drug development to enable information helpful to the development of AST devices to be generated during the clinical trials for the drug product. This approach may be broadly applicable to various types of AST devices, including AST broth dilution panels, disc diffusion, or gradient diffusion devices used with antimicrobial test systems, or new or existing molecular-based devices that can identify mutations associated with decreased antimicrobial susceptibility. The nature of these interactions can take many forms and need not be restricted to a single device manufacturer. The availability of a drug to multiple device manufacturers for use during AST device

development may increase clinical laboratories' access to AST devices at the time of drug approval or shortly thereafter.

IV. Considerations for Coordinated Development of Antimicrobial Drugs and AST Devices

Coordinated development of antimicrobial drugs and AST devices depends on agreements between the antimicrobial drug sponsor and AST device manufacturer. We recommend that if proceeding with coordinated development, both the drug sponsor and AST device manufacturer submit their coordinated development plans to CDER and CDRH, respectively, for review and comment.[3] FDA also welcomes joint meetings with the drug sponsor and device manufacturer and personnel from both CDER and CDRH to address issues that affect the coordinated development of both the drug and AST device. Usually such meetings would be requested by an AST device manufacturer through the CDRH pre-submission process, which can also be used to obtain recommendations regarding the AST device under development. The CDRH pre-submission process should be used to communicate with CDRH plans for coordinated development of antimicrobial drugs and AST devices. In addition, drug sponsors should submit such information in their investigational new drug application (IND).

In general, an investigational device exemption (IDE) is not needed for the investigation of AST devices if the requirements and conditions of 21 CFR 812.2(c)(3) are met. However, if the AST device under development (e.g., a rapid susceptibility testing device) is to be used for clinical trial enrollment, an IDE may be needed for the device (21 CFR part 812).[4] This should also be discussed with CDRH through the pre-submission process.

If coordinated development of a drug and an AST device is pursued, CDRH can communicate with CDER and review the 510(k) submission during the NDA review process, to maximize the likelihood that AST device clearance can occur either coincident with or shortly after drug approval. For device clearance to occur either coincident with or shortly after drug approval, the AST device 510(k) submission should be submitted early enough to allow sufficient time for FDA to complete its review. In the 510(k) submission, appropriate permissions to FDA from the drug sponsor to cross-reference information from the NDA should be provided in the 510(k) submission to facilitate AST device review.

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[3] CDRH feedback on device development can be obtained through the pre-submission program. See *Guidance for Industry and Food and Drug Administration Staff, Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff*, available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf. Information regarding the CDER pre-IND consultation program for the Office of Antimicrobial products is available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/default.htm.

[4] For IND requirements applicable to drug development, please consult IND regulations and relevant CDER materials, such as "Development & Approval Process (Drugs)," available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm.

Despite coordinated development, FDA will continue to make review decisions for the antimicrobial drug product and the AST device independently, i.e., coordinated development of the antimicrobial drug product with an AST device would have no effect on our reviews, review timelines, or approval or clearance of either product, other than facilitating clearance of the AST device coincident with or shortly after drug approval, as appropriate.